REMARKS

This Amendment is in response to the Examiner's Office Action mailed on March 11, 2005. Claims 1-44, 48 and 55 have been canceled without prejudice to later filing in an application. Claims 45 and 61 have been amended. Support for the claim language "non-myeloablative" appears in the Specification, for example, at page 36, line 26. Claims 45-47, 49-54, and 56-86 are now pending in the application.

Reconsideration of the application is respectfully requested in view of the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

I. Rejection under 35 U.S.C. §112, First Paragraph

Claims 58-69 and 71-86 stand rejected under 35 U.S.C. §112, First paragraph as failing to comply with the enablement requirement. Applicants respectfully traverse the Examiner's rejection based on the following reasons.

Pursuant to MPEP 2164.04, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). MPEP further provides that

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Independent claim 58 is directed to a method of using pentostatin for GVHD prophylaxis, i.e., for preventing or reducing the risk of developing GVHD in a patient who is a recipient of an organ or tissue transplant. As specified by claim 58, pentostatin in a pharmaceutically effective amount is administered to a transplant recipient within a predetermined time window after the transplantation.

The specification provides ample description of how to use pentostatin to prevent or reduce GVHD in a transplant recipient. For example, as described in the section entitled "GVHD prophylaxis" starting at page 36, pentostatin can be administered to the recipient following various dosing regimens. The specification further teaches that pentostatin can be administered to a transplant recipient after the transplantation at 0.5-1.5 mg/m^2/day on days +8, +15, +12 and +30 following stem cell infusion.

The Examiner has not met the burden of providing a reasonable explanation as to why a skilled artisan in the relevant field of tissue/organ transplantation would not know how to use pentostatin to prevent or reduce the rate of GVHD of transplant recipients without undue experimentation in view of Applicants' teaching in the specification.

However, in an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection Applicants submit herewith a declaration by Dr. Joi Ninomoto under 37 CFR §1.132 to show that according to the regimens described in the specification clinical trials of pentostatin have been conducted for GVHD prophylaxis in transplant recipients. As described in details the attached Declaration of Dr. Ninomoto, 73 patients who received hematopoietic stem cell transplants enrolled in a randomized phase I/II clinical trial. The results of the trial demonstrate that pentostatin is efficacious in preventing and/or reducing GVHD in transplant recipients without interference with engraftment. In the trial patients receiving pentostatin at the dose of 1.5 mg/m^2 had the lowest number of incidents of developing grade II-IV aGVHD (failure rate of 29% vs. 47% in the control group). In other words, acute GVHD was prevented or reduced in 70% of the patients treated with pentostatin without severe toxicity and delay of engraftment.

In view of the teaching in the specification and the significantly higher success rates in pentostatin treatment arms than that in the control group, Applicants submit that the claimed method of using pentostatin to prevent or to reduce GVHD in a transplant recipient is sufficiently enabled under 35 U.S.C. §112, First paragraph. Withdrawal of this ground of rejection is therefore respectfully requested.

II. Rejection under 35 U.S.C. §103(a)

The Examiner maintained the rejection of claims 45-54 and 56 under 35 U.S.C. §103(a) as being unpatentable over Waller (U.S. Pat. No. 5,800,539) in combination with Trotta et al.

(Cancer Research (1981) 41:2189-2196); and Spaner (U.S. Pat. No. 6,258,257). The Examine also rejected claims 57 and 70 under 35 U.S.C. §103(a) as being unpatentable over Waller (U.S. Pat. No. 5,800,539) in combination with Trotta et al. (Cancer Research (1981) 41:2189-2196).

Independent claim 45 as amended specifies a method for preventing or reducing the risk of developing GVHD in a human patient who is a recipient of an organ or tissue transplant. The method includes treating the patient with myeloablative conditioning regimen; and administering to the transplant recipient pentostatin in a pharmaceutically effective amount of about 1-10 mg/m^2 or about 0.05-5 mg/m^2 within a predetermined time window before the transplantation.

None of the cited references teaches or suggests such GVHD prophylaxis using pentostatin in a pharmaceutically effective amount of about 1-10 mg/m^2 or about 0.05-5 mg/m^2, let alone teaching or suggesting treating the patient with myeloablative conditioning regimen. In contrast, Waller et al. is not even related to pentostatin, disclosing instead treating transplant recipients with mononuclear cells that have been treated with cytotoxic chemotherapeutic drugs to render them incapable of proliferating, such as mitomycin C, bleomycin, fludarabine, and doxirubicin (column 5, lines 1-15; Abstract; and column 4, lines 66-67; column 5, line 1).

On the other hand, Trotta et al. discloses a study of immunosuppressive effects of constant infusion of 2'-deoxycoformycin (i.e., pentostatin or DCF) in mice at a constant rate of 0.4 mg/Kg body weight (which would be approximately 15 mg/m^2 for an adult patient) per day for 5 days. Page 2190, column 1, 3rd paragraph. Thus, Trotta et al. also fails to teach or suggest the claimed method of preventing GVHD in human patients. In addition, Spaner merely teaches that current methods to prevent and treat GVDH involve administration of drugs such as cyclosporin-A and corticosteroids (column 1, lines 49-53). Thus, none of the cited references, independently or in combination, discloses every element of the claimed invention.

To establish a prima facie case of obviousness, the Examiner bears the burden of proving 1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; 2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and 3) one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success of the claimed invention. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F. 2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and *In re Dow Chem.*, 837 F. 2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

As discussed above, the cited references neither disclose all of the claim limitations nor suggest that Waller's method of administering chemotherapeutic agent-treated mononuclear cells to a transplant recipient be modified in view of Trotta's disclosure of immunosuppressive effects of pentostatin. Further, Trotta et al. merely hypothesized that pentostatin might be used to promote transplantation across major histocompatibility barriers (page 2194, column 2, last paragraph). In view of the completely different approaches taken by Waller (administration of chemo-treated mononuclear cells) and Trotta (infusion of a high dose of 0.4 mg/Kg pentostatin into mice), one of ordinary skill in the relevant field of tissue/organ transplantation would not have a reasonable expectation of success without specific guidance as to how to use the pentostatin, as taught by Applicants in the instant application.

In addition, as shown in Dr. Ninomoto's Declaration, under the treatment regimens described in the specification clinical trials of pentostatin have been conducted for GVHD prophylaxis in transplant recipients. About 70% of the patients who received pentostatin at a pharmaceutically effective dose did not develop or had a reduced rate of GVHD. Also significantly, administration of pentostatin did not delay engraftment in the patients.

In view of pharmaceutical advantages of pentostatin in GVHD prophylaxis and the absence of teaching or suggestion of the claimed method in the cited references, Applicants submit that the claimed invention is not only novel but also non-obvious under 35 U.S.C. 103(a). Withdrawal of rejection is therefore respectfully requested.

CONCLUSION

In light of the remarks and arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 12636-219).

Respectfully submitted,

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